The splicing regulator PTBP1 controls the activity of the transcription factor Pbx1 during neuronal differentiation.

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Public Summary:
The neurons that transmit information around the nervous system develop in several stages. Embryonic stem cells specialize to form neuronal progenitor cells, which then develop into neurons. These cell types have different characteristics, in part because they make different proteins, or different versions of the same proteins. To make a protein, the DNA sequence of a gene is used to build a molecule of ribonucleic acid (RNA) that acts as a template for the protein. However, not all of this sequence codes for the protein. The non-coding regions must be removed from the RNA, and the remaining “exons” joined together to form the final “mRNA” template. Not all of the exons are necessarily included in the final mRNA molecule. By joining together different combinations of exons, several different versions of a protein can be produced from a single gene. This process is known as alternative splicing. One way that alternative splicing is controlled is through proteins that bind to RNA and determine which exons are included or excluded from the final mRNA molecule. PTBP1 is an RNA-binding protein that controls alternative splicing in embryonic stem cells and neuronal progenitor cells. Embryonic stem cells have the special property of being able to develop into all the cells of the body. In contrast, neuronal progenitor cells are restricted in their development and only give rise to specialized cells of the nervous system. The role of PTBP1 in these properties was not clear. Linares et al. have now used a range of techniques to study the RNA molecules produced in these two cell types and how these RNAs change when PTBP1 is removed. This identified many RNAs whose splicing is regulated by PTBP1, including mRNAs of the Pbx1 gene that produces an important regulator of neuronal development. Further investigation revealed that PTBP1 prevents a particular exon being included in the mRNA template for Pbx1. This creates an embryonic stem cell form of Pbx1 that does not affect neuronal genes. Removal of PTBP1, allows splicing of the Pbx1 exon and produces a version of Pbx1 that is found in neuronal progenitor cells and which turns on neuronal genes. Thus, through its action on Pbx1, one role of PTBP1 is to enable stem cells to maintain their non-neuronal properties and prevent their premature development into neuronal progenitor cells. Pbx1 is only one of many genes controlled by PTBP1 at the level of splicing. One challenge for the future will be to understand how these many genes work together in a common program that determines the properties of stem cells. Another question regards how the different Pbx1 proteins in stem cells and in neuronal progenitors can exert different effects in the cells where they are made.

Scientific Abstract:
The RNA-binding proteins PTBP1 and PTBP2 control programs of alternative splicing during neuronal development. PTBP2 was found to maintain embryonic splicing patterns of many synaptic and cytoskeletal proteins during differentiation of neuronal progenitor cells (NPCs) into early neurons. However, the role of the earlier PTBP1 program in embryonic stem cells (ESCs) and NPCs was not clear. We show that PTBP1 controls a program of neuronal gene expression that includes the transcription factor Pbx1. We identify exons specifically regulated by PTBP1 and not PTBP2 as mouse ESCs differentiate into NPCs. We find that PTBP1 represses Pbx1 exon 7 and the expression of the neuronal Pbx1a isoform in ESCs. Using CRISPR-Cas9 to delete regulatory elements for exon 7, we induce Pbx1a expression in ESCs, finding that this activates transcription of neuronal genes. Thus, PTBP1 controls the activity of Pbx1 to suppress its neuronal transcriptional program prior to induction of NPC development.